Journal of Controlled Release, 27 (1993) 149–156
Elsevier Science Publishers B.V.

COREL 00897

Film coating of pellets with insoluble polymers obtained in situ crosslinking in the fluidized bed

C.B. Abletshauser, R. Schneider and H. Rupprecht

Department of Pharmaceutical Technology, University of Regensburg, Regensburg, Germany

Received 15 December 1992; accepted in revised form 18 June 1993

A novel technique for the manufacture of water-insoluble film coatings on drug-loaded saccharose pellets is described. The method is based on the simultaneous spraying of aqueous solutions of a film-forming polymer and an appropriate crosslinking agent. Crosslinking of the polymer was achieved in situ in the film during coating of the pellets in a fluidized bed. Uniform film coatings were formed without additives. Pan coating with sequential spraying of the components yielded similar results, however, it was more time consuming.

The anionic polymer, sodium alginate, was combined with different cationic crosslinking agents, such as calcium ions, aluminum ions, Cetrimide (tetradecyltrimethylammonium bromide), and Eudragit E (copolymer of dimethylaminoethylmethacrylate and neutral methacrylic acid esters) (in 0.1 N HCl) in aqueous solutions. The swelling behavior of the cast films in water depended on the crosslinking component and the film thickness. For studying the in vitro drug release through the film coatings, the pellets were drug-loaded with acetaminophen and indomethacin as model drugs. Alginate films crosslinked with calcium ions showed the most promising features for controlled drug release.

The release rate of the model drug acetaminophen proved to be almost independent of the pH of the dissolution fluid (pH 7.4 phosphate buffer, 0.1 N HCl). During drug release, the coatings did not disintegrate in 0.1 N HCl, but slowly disintegrated in buffer solution. Indomethacin was released at considerably smaller rates.

Key words: Pellet coating; Spray technique; Alginate; Crosslinking; Fluidized bed; Controlled release

Introduction

Film coating of pellets or tablets with water-insoluble substances is usually based on organic solutions of the film-forming material or on aqueous colloidal dispersions of polymer particles (latices or pseudolatices) [1,2]. During the last years, the use of organic solvents has been considerably reduced due to hazardous environmental problems [3]. The alternative aqueous latexes usually require different additives such as surfactants, plasticizers and antisticking agents for the manufacture, stabilisation and application of the dispersion. These ingredients can influence the quality of the final products [2,4]. Therefore, alternative methods are generally interesting.

In this study a film coating method is described, based on the reaction of two water-sol-

Correspondence to: Prof.Dr. Herbert Rupprecht, Lehrstuhl fur Pharmazeutische Technologie, Universität Regensburg, Universitatsstr. 31, D-8400 Regensburg, Germany.

uble components forming in situ insoluble films. Promising features for the formation of insoluble polymer films show the interactions between the polyanions of alginate and crosslinking cations such as calcium ions. For example this reaction is used to produce microcapsules, microparticles or matrix systems [5,6].

Based on this complex formation a special spray technique was developed to form alginate complexes with crosslinking agents such as $CaCl_2$, $AlCl_3$, Cetrimide, or Eudragit E on drug-loaded pellets by simultaneous or alternating spraying. Pan or fluidized bed equipment are used to achieve an uniform distribution of the components and a fast drying of the sprayed films.

Materials and methods

Materials

The following materials were obtained from commercial suppliers and used as received: saccharose pellets, 3 mm diameter (Iso-Werk, D-Regensburg); sodium alginate-Protanal SF 250, the viscosity of a 1% (w/w) solution at 20°C was 165 mPa s (Protan GmbH, Drammen, Norway); Cetrimide (tetradecyltrimethylammonium bromide), calcium chloride, aluminum chloride, methanol, potassium dihydrogenphosphate all of analytical grade (E. Merck, D-Darmstadt); Eudragit E (copolymer of dimethylaminoethylmethacrylate and neutral methacrylic acid esters) (Röhm Pharma, D-Darmstadt); acetaminophen (Hoechst AG, D-Frankfurt a.M.); indomethacin (Pfannenschmidt, D-Hamburg); water: Aqua ad iniectabilia DAB 10 (double distilled).

Methods

Drug loading of saccharose pellets by solvent deposition

Drug solutions (acetaminophen 3%, 500 ml; indomethacin 1.5%; 1000 ml) in methanol were sprayed onto pellets (1000 g) in a coating pan with air supply (Erweka, D-Heusenstamm). Pan diameter = 25 cm; pan speed = 30 rpm; spraying rate = 9 ml min^{-1}; air inlet temperature = 80°C. Final drug content: acetaminophen 6.4 mg/g; indomethacin 12.5 mg/g

Film formation on pellets

(a) Sequential spraying with a pan coating technique Pan stainless steel, diameter = 1[illegible] cm; pan speed = 30 rpm; air inlet temperature = 62° load = 120 g. Formation of one film layer aqueous Na-alginate solution (1%, 300 ml) and aqueous solutions of crosslinking agent 50 ml ($CaCl_2$ 1.7%; $AlCl_3$ 1.8%; Eudragit E 1.0% 0.1N HCl) or 9 ml (Cetrimide 5.7%) were intermittently sprayed on the pellets, rate = 1 ml min^{-1} [7].

(b) Simultaneous fluidized bed spraying Fluidized bed coater Aeromatic Strea (Aeromatic, CH-Muttenz) with two spray nozzles (Fig. 1). Aqueous solutions of sodium alginate (1.0%) and crosslinking agent ($CaCl_2$ 0.2 and 0.52%) were simultaneously sprayed on 2C g drug-loaded pellets. Air inlet temperature = 80°C; air outlet temperature = 55-60°C Spray rates: sodium alginate soln. = 9 ml min^{-1} $CaCl_2$ soln. = 4.5 ml min^{-1}.

Film thickness measurement

The dried, coated pellets were cut and the wall thickness measured with a light microscope (Epi Lux, Leitz, D-Wetzlar). For the measurement of the swollen coats, film samples were evaluated after dissolution of the saccharose core material and measured as described above.

In vitro drug release

Drug release was studied by the paddle method USP XXII. 1–2 g pellets, 50 rpm, $n = 3$; 500 ml dissolution fluid (37°C): H_2O, 0.1 M HCl (ionic strength = 0.1), simulated intestinal fluid without enzyme (pH 7.4 phosphate buffer, ionic strength = 0.088) or pH 7.2 aqueous phosphate buffer (buffer/water = 1+4, ionic strength = 0.017) (USP XXII). Drug detection: monitor circuit with peristaltic pump (Minipuls 2, Gilson, Villiers-le-Bel, France), UV-photometer (LKB Ultraspec II, LKB, D-Freiburg) with flow

through quartz cell $d = 10$ mm ([redacted]aminophen at 243 nm, indomethacin at 318 nm); data processing by Olivetti PC M 24, software for drug release monitoring N. Lill, Hoechst AG, D-Frankfurt.

Results and discussion

The in situ formation of water-insoluble alginate films by alternating or simultaneous spraying of alginate and crosslinking agent solutions yields homogeneous, smooth coatings on drug-loaded saccharose pellets. Calcium and aluminum ions crosslink the alginate by electrostatic interactions with the carboxylate groups of neighbouring macromolecules [8]. Eudragit E, a poly (methylmethacrylate) with charged amino groups in acidic solution, may also react by electrostatic forces between the oppositely charged macromolecules forming a three-dimensional polymer network. Cetrimide is bound through its strong basic quaternary amino groups to the alginate carboxylate groups also via electrostatic forces and thus becomes insoluble in water. Crosslinking of the alginate may then occur through hydrophobic forces between the alkyl chains of Cetrimide molecules bound to alginate carboxylate groups [9].

The concentrations of the crosslinking agents were calculated from the charge equivalents of the alginate carboxylate groups. Using the pan coating technique, Ca^{2+}, Al^{3+} and Eudragit E were added in a 1:1 ratio of their charge equivalents and the alginate carboxylate groups. Due to technical problems Cetrimide was used in an equivalent ratio of 1:10. Higher amounts of this agent resulted sticking and inhomogeneous films on the pellets.

The coatings were build up in several layers: one layer was deposited by alternating spraying of 300 ml sodium alginate and 50 ml crosslinking agent solution (9 ml Cetrimide soln.) on 120 g pellets followed by a drying period. After seven steps the thickness of the dry coatings varied between 90 μm for Cetrimide-alginate and 135 μm for aluminum-alginate, with 120 μm for calcium-alginate in between. Twelve layers were necessary to obtain a layer thickness of 85 μm for the Eudragit E-alginate film.

With an equal amount of alginate the pan coating technique yields films with a different thickness and swelling behavior in water, depending on the crosslinking agent (Table 1). In contact with water, limited swelling (no dissolution) was observed with a specific influence of the crosslinking agent on the swelling process. With a ratio of wall thickness in the swollen and in the dry state of 1.3, the Eudragit E-alginate film shows the smallest degree of swelling. It can be assumed that hydrophilic groups on both macromolecular film components have lost their accessibility for water molecules due to their mutual interactions. Alginate crosslinked by the multivalent inorganic ions of calcium or aluminum is more accessible for water, expressed through ratios of wall thickness in the dry and swollen state of 1.6 and 1.8, respectively. The strongest swelling is shown by the Cetrimide-alginate film with a ratio of 2.8, indicating that the crosslinking of the alginate molecules through Cetrimide is very weak and/or flexible.

The in vitro dissolution of acetaminophen from pan-coated pellets is characterized by the $t_{50\%}$ and $t_{90\%}$ release times in water, 0.1 M HCl, and pH 7.4 buffer solution (Table 2).

Acetaminophen is released more rapidly from the Eudragit-alginate coated pellets in all dissolution fluids, with a $t_{90\%}$ of around 30 min. The drug is also rapidly released from Cetrimide-alginate coated pellets with a $t_{90\%}$ in the range of

Table 1
Weight increase and wall thickness of pellets coated with different alginate films

Crosslinking agent	Weight increase (%)	Wall thickness (μm)	
		swollen	dried
$CaCl_2$ (7 layers)	18.5	190	120
$AlCl_3$ (7 layers)	19.0	245	135
Cetrimide (7 layers)	28.0	255	90
Eudragit E (12 layers)	42.0	110	85

Table 2
Acetaminophen release from pellets with different alginate coatings

Coating	$t_{50\%}$ (min)	$t_{90\%}$ (min)	Dissolution medium
Bare pellets	<2	<2	distilled water
Calcium alginate (7 layers)	70	200	distilled water
	37	75	0.1 N HCl
	54	115	pH 7.4 buffer
Aluminum alginate (7 layers)	28	90	distilled water
	42	80	0.1 N HCl
	23	73	pH 7.4 buffer
Cetrimide alginate (7 layers)	20	45	distilled water
	15	40	0.1 N HCl
	17	37	pH 7.4 buffer
Eudragit E alginate (12 layers)	11	27	distilled water
	11	27	0.1 N HCl
	10	37	pH 7.4 buffer

40 min, while aluminum-alginate and, in particular, calcium-alginate coated pellets show a significantly slower release with a $t_{90\%}$ between 73 and 200 min.

In 0.1 M HCl, the acetaminophen release tends to be faster than in water from pellets coated with calcium alginate (discussed later) and Cetrimide-alginate, while Eudragit and Al^{3+} crosslinked alginate coatings yield almost the same release as in water. In pH 7.4 buffer solution, the Ca^{2+} crosslinked alginate coating shows the most retarding effect on acetaminophen release, compared with coatings crosslinked with aluminum, Cetrimide, and Eudragit.

The different rates of acetaminophen release from the alginate coated pellets are due to the barrier function of the polymer film in the swollen state. Polymer networks with a smaller content of crosslinking bridges are stronger hydrated and impose a smaller resistance against disintegration and erosion. The inorganic, multivalent ions seem to build up a stronger and more resistant polymer network than the organic crosslinking substances. The Ca^{2+} crosslinked alginate coating is most promising for a controlled release of drug from the saccharose pellets. However, the pan coating technique used for the production of alginate-crosslinked films is very time consuming because of the low spraying rates of the solutions and the long drying periods. More than 25 h were necessary to produce films with a thickness of around 100 μm.

Therefore, the attention was focussed on the fluidized bed technique. Apart from the more effective and faster drying process, simultaneous spraying of the film components can easily be realized by means of two nozzels, mounted in the lower part of the fluidized bed (Fig. 1). Concluding from the results mentioned above, calcium ions were selected as crosslinking agent for the further improvement of the in situ film formation of insoluble alginate films.

The calcium alginate coated pellets show a macroscopic smooth and homogeneous surface (Fig. 2). Microtablets as model core material (diameter = 2 mm, compressed microcrystalline cellulose) could be equally coated without edge splitting or cracking of the polymer film.

For a more rapid coating, a higher concentrated alginate solution (7%) of the same viscosity grade as the described 1% solution (Protanal

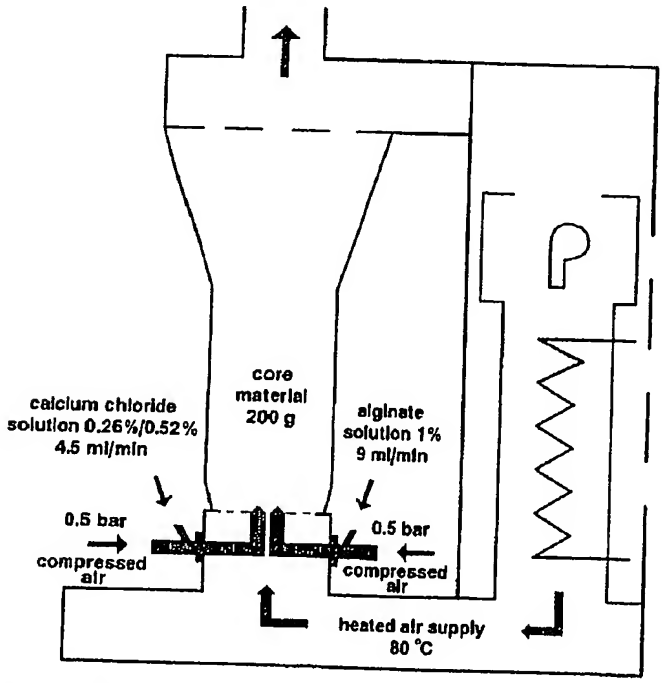

Fig. 1. Simultaneous spraying of sodium alginate and calcium chloride solution in a modified aeromatic fluidized bed coater.

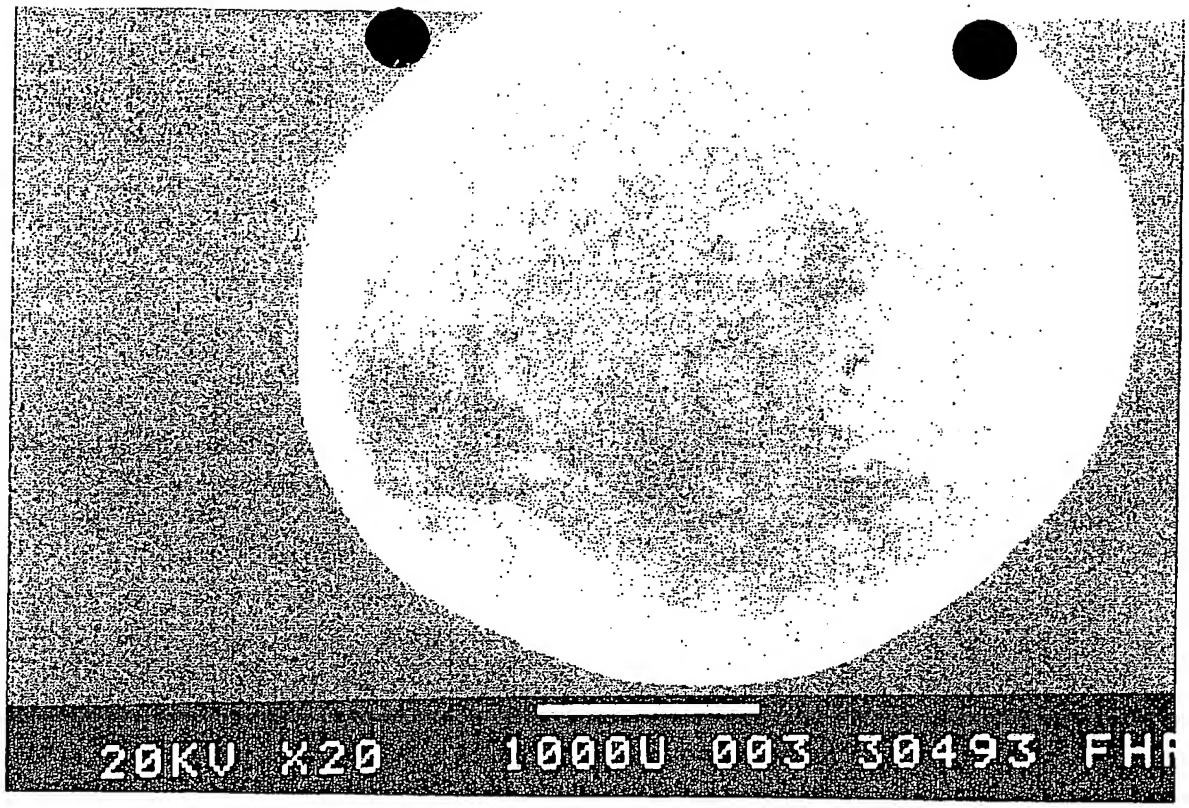

Fig. 2. Scanning electron micrograph of a calcium alginate coated saccharose pellet manufactured by the fluidized bed technique (wall thickness= 80 μm; magnification=20x; bar= 1000 μm).

LFR 50/60, a low molecular weight alginate) gave similar results.

In comparison with methods, which prepare beads by a dropping technique or which coat tablets by dipping the core material into the polymer solution, the present technique can be used for different core materials in a continuous, well-controlled process [6,10]. However, considering the high air inlet temperature for a rapid coating, temperature-sensitive drugs may be degraded.

The acetaminophen release in water from saccharose pellets coated with calcium-alginate either by the pan coating or by the fluidized bed technique is compared in Fig. 3. Coatings produced with the same wall thickness (80 μm) and the same alginate/Ca^{2+} ratio show very similar release patterns in water with a tendency for slower release from pan coated pellets.

If an equivalent ratio alginate:calcium of 2:1 is applied, drug release is considerably slower after dissolution of 30% of the drug. This may be due to the lower content of pore-forming sodium

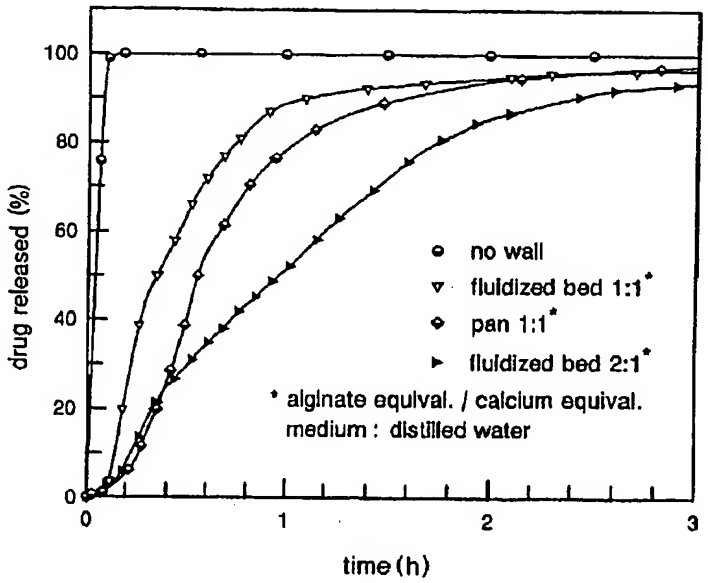

Fig. 3. Acetaminophen release from calcium alginate pellets (wall thickness 80 μm) prepared by different methods ($n=3$; $c<4\%$).

chloride produced as by-product of film formation and the different swelling behavior of this coating compared with calcium alginate 1:1. In

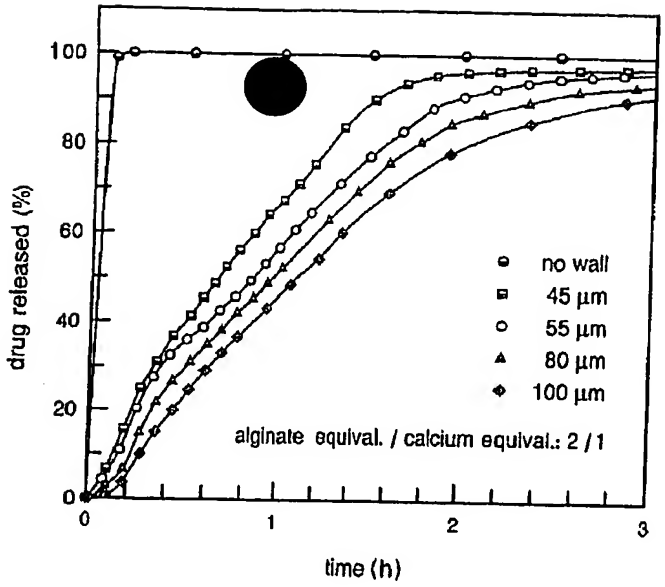

Fig. 4. Acetaminophen release from calcium alginate pellets in distilled water as a function of wall thickness ($n=3$; $c<4\%$).

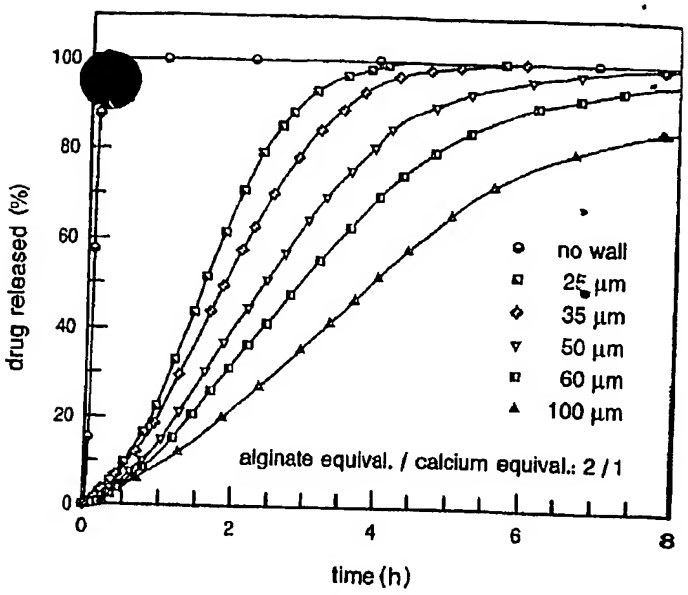

Fig. 6 Indomethacin release from calcium alginate pelle as a function of wall thickness ($n=3$; $c<4\%$). Test solution: pH 7.2, buffer/water (1+4).

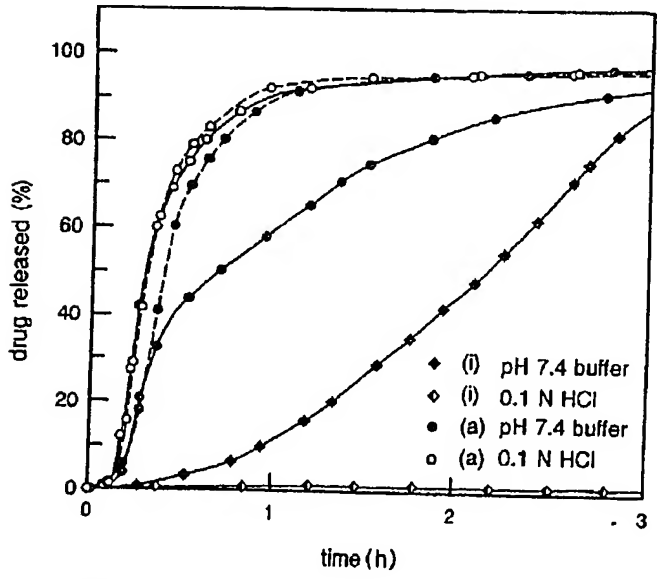

Fig. 5. Release of indomethacin (i) and acetaminophen (a) from calcium alginate pellets (wall thickness 100 µm) in different test solutions ($n=3$; $c<4\%$). Alginate equival./calcium equival.: 1 / 1 (---); 2 / 1 (—).

the lower crosslinked 2:1 coatings, the polymer network becomes more hydrated in contact with water and pores can be closed in the film. The number of crosslinking bridges seems to be sufficient so that the swelling process cannot enhance disintegration of the coatings during the drug release. Therefore, the 2:1 films impose a higher barrier for drug diffusion, similar to swelling hydrocolloid matrix systems [11].

The influence of wall thickness of the coatings on drug release is shown in Fig. 4 for pellets coated with calcium-alginate (equivalent ratio alginate : calcium = 2:1). The release pattern, almost linear for more than 70% drug released, indicates a moderately decreasing drug release rate with increasing wall thickness with a $t_{50\%}$ value of 40 min at 45 µm and 64 min at 100 µm. A small but significant lag time at the beginning of the dissolution indicates that the coatings obtained by the fluidized bed technique do not contain large pores or other defects.

Indomethacin was selected as a model drug with pH-dependent solubility. The saccharose pellets were loaded with the drug using the same solvent deposition technique as described above. In artificial gastric juice 0.1 M HCl, indomethacin is only marginally released, in contrast to acetaminophen (Fig. 5). In this dissolution fluid, the solubility of indomethacin, a weak acid with a pK_a of 4.5, is very poor ($c_s<50$ µg/ml at 37°C). Therefore, the release rate is mostly determined by the dissolution process of the drug and not significantly influenced by diffusion through the coating.

The acetaminophen release pattern of calcium-alginate 1:1 coatings tends to be similar in

the different test solutions. In contrast, coatings manufactured with an equivalent ratio of 2:1 (alginate:calcium) show a slower drug release in pH 7.4 buffer than in acidic solution. This behavior may occur from the higher swelling of this polymer film, mentioned above. In 0.1 M HCl, the calcium alginate is transformed into alginic acid with the loss of electrostatic repelling forces of carboxylate groups and the loss of hydration. Indeed, the coatings stay intact in this medium but their barrier function decreases because of the contracted polymer network. In pH 7.4 buffer solution, the calcium ions are exchanged by monovalent ions of the medium thus causing swelling and slow disintegration.

Compared with acetaminophen the indomethacin release in pH 7.2 aqueous buffer solution (c_s= 1.0 mg/ml at 37°C) is characterized by a slow release rate at the beginning. Increasing wall thickness of the calcium-alginate film decreases the drug release rate and enhances the sigmoidal character of the dissolution curve (Fig. 6). For this less soluble drug, the release rates can be adjusted by varying the wall thickness over a wide range with $t_{50\%}$ of 100 min at 25 μm and $t_{50\%}$ of 240 min at 100 μm. Drug release patterns of calcium alginate-coated pellets stored for 6 month (20°C at 45% R.H.) did not indicate ageing processes under these conditions.

Conclusions

- The in situ formation of insoluble film coatings on the surface of drug-loaded pellets can be obtained by simultaneous fluidized bed spraying of aqueous solutions of the film-forming and crosslinking components.

- Calcium chloride proved to be the most suitable crosslinking agent for manufacturing insoluble alginate films based on electrostatic interaction between the polyanion and salt-forming cation, compared with $AlCl_3$, Eudragit E, and Cetrimide.

- The composition and thickness of the films can easily be varied and reproduced by the applied technique. The coatings are homogeneous and exhibit smooth surfaces. Even thinfilms (thickness ≃20 μm) donot contain large pores or other defects.

- The film formation process can be controlled without problems of tackiness, cracking,peeling and edge splitting (core material microtablets) of the coatings.

- Calcium-alginate films significantly sustain the drug release from the pellets both in acidic (pH 1.2) and weak alkaline (pH 7.4) dissolution fluids. Drug release rates are considerablylower for indomethacin than for acetaminophen, according to the different solubilityproperties of these drugs.

- In situ formation of insoluble films by fluidized bed spraying of aqueous solutions of the film components without any ingredients shows promising features for further improvement of the method and can be extended to a variety of film-forming substances such as ionic and nonionic polysaccharides, proteins etc.; each combined with a specific crosslinkingagent.

Acknowledgement

The support of the following was greatly appreciated; the Fond der Chemie, Frankfurt; Iso-Werk, Regensburg; E. Merck, Darmstadt; Rohm Pharma, Darmstadt; Henkel, Düsseldorf.

References

1 S.C. Porter and C.H. Bruno, Coating pharmaceutical solid-dosage forms, in: A.Lieberman, L. Lachman and J.B. Schwartz (Eds.), Pharmaceutical Dosage Forms, Marcel Dekker, New York, 1990, Vol. 3, pp. 77–160.

2 J.W. McGinity, Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, Marcel Dekker, New York, 1989.

3 J.E. Hogan, Aqueous versus organic solvent coating, Int. J. Pharm. Technol. Prod. Mfr., 3 (1982) 17,b120.

4 K.H. Bauer, K. Lehmann, H.P. Osterwald and G. Rothgang, Überzogene Arzneiformen, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1988.

5 R. Bodmeier and O. Paeratakul, A novem multiple-unit sustained release indomethacin-hydroxypropyl methylcellulose delivery system prepared by ionotropic gelation of sodium alginate at elevated temperatures, Carbohydr. Polym., 16 (1991) 399–408.

6 N. Segi, T. Yotsuyanagi and K. Ikeda, Interaction of calcium-induced alginate gel bead swith propanolol, Chem. Pharm. Bull., 37 (1989) 3092–3095.

7 R. Schneider, Polymeradsorbate und Polymerhüllen zur Beeinflussung der Wir[redacted]liberation, Dissertation, Universität Regensburg, [redacted].

8 D.A. Rees, Polysaccharide shapes and their interactions: Some recent advances, Pure & Appl. Chem. 53 (1981) 1–14.

9 A.J. Dualeh and C.A. Steiner, Structure and properties of surfactant-bridged viscoelastic gels, in: R.S. Harland and R.K. Prud'homme (Eds.), ACS Symp., WA, 1992, pp. 42–52.

10 H.R. Bh[redacted], R.W. Mendes, E. Mathiowitz and H.N. Bharga[redacted] novel, self-correcting membrane coating technique. Pharm. Res. 8 (1991) 576–583.

11 N.A. Peppas. Swelling controlled release systems: recent developements andapplications, in: B.W. Müller (Ed), Controlled Drug Delivery, Wissenschaftl. Verlagsgesellschaft, Stuttgart, 1987, pp. 161-173.